Universidade de Aveiro Secção Autónoma das Ciências da Saúde

2015

MARIANA JOSÉ MANUEL IN-UBA

RELATÓRIO DE ESTÁGIO CURRICULAR: 7 MESES COMO COORDENADORA DE ESTUDOS NA BLUECLINICAL LDA.

CURRICULAR TRAINING REPORT: 7 MONTHS AS A STUDY COORDINATOR AT BLUECLINICAL LTD.

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau do Mestre em Biomedicina Farmacêutica sob a orientação da Doutora Cristina Lopes, Diretora de Operações Clínicas da Blueclinical Lda. e também do Professor Doutor José Carlos Fontes das Neves Lopes, Professor Auxiliar do Departamento de Física da Universidade de Aveiro.

“I have no special talent. I am only passionately curious.”

Albert Einstein

o júri

presidente

Doutor Bruno Miguel Alves Fernandes do Gago
Professor Auxiliar Convidado, Universidade de Aveiro

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palavras-chave Coordenação de estudos, ensaios clínicos, estudos observacionais, investigação e desenvolvimento, investigação clínica, Biomedicina Farmacêutica

resumo

O presente relatório descreve de forma detalhada as atividades realizadas no âmbito da coordenação de estudos clínicos e observacionais durante o estágio curricular na empresa Blueclinical Lda., inserido no Mestrado de Biomedicina Farmacêutica.

A empresa Blueclinical Lda. opera em três áreas distintas: consultadoria em investigação e desenvolvimento, gestão e coordenação dos centros de ensaio, e unidade de Fase I.

O estágio curricular teve a duração de sete meses ao longo dos quais tive a possibilidade de executar diferentes tarefas relacionadas com a coordenação de ensaios clínicos no Centro Hospitalar do Baixo Vouga, E.P.E., em Aveiro (CHBV).

Este estágio curricular permitiu-me desenvolver competências teóricas e práticas em matéria de coordenação de ensaios clínicos e estudos observacionais. Também tive a oportunidade de aprofundar o conhecimento que adquiri ao longo do meu percurso académico. Durante esta experiência, eu tive ainda oportunidade de interagir com diversos profissionais de saúde e desenvolver o meu conhecimento no campo de diferentes indicações terapêuticas. Também pude interagir com vários monitores e promotores. Esta experiência permitiu-me desenvolver as minhas competências relativas à gestão de tempo, comunicação e resolução de problemas.

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keywords coordination of studies, clinical trials, observational studies, R&D, clinical investigation, Pharmaceutical Medicine

abstract

The present report describes in detail the activities undertaken under the coordination of clinical and observational studies during the curricular internship at Blueclinical Ltd., inserted in the Master of Pharmaceutical Biomedicine.

Blueclinical Ltd.company operates in three different areas: R&D consultancy, management and coordination of trial centers, and a phase I unit.

The curricular internship had the duration of seven months during which I was able to perform different tasks relating to coordination of clinical trials in *Centro Hospitalar do Baixo Vouga, E.P.E.*, (CHBV) in Aveiro, Portugal.

This academic internship allowed me to develop theoretical and practical skills in the field of clinical trials and observational studies. I also had the opportunity to further the knowledge I gained throughout my academic journey. During this internship, I had the opportunity to interact with different health professionals and develop my knowledge in the field of several therapeutic indications. I also could interact with distinct monitors and sponsors. This experience allowed me to improve time management, communication and problems resolution skills.

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List of Abbreviations

AE	Adverse Event
CEIC	Comissão de Ética para a Investigação Clínica *(Ethics Committee for Clinical Research)*
CHBV	Centro Hospitalar do Baixo Vouga
CHMP	Committee for Medicinal Products for Human Use
CNPD	Comissão Nacional de Proteção de Dados (*National Committee for Data Protection)*
CRA	Clinical Research Associate
CRO	Contract Research Organizations
CRF	Case Report Form
CRP	Clinical Research Partnership
CSC	Clinical Study Coordinator
CT	Clinical Trial
CTA	Clinical Trial Application
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GAEC	Gabinete de Apoio aos Ensaios Clínicos *(Clinical Trials Support Office)*
GDP	Gross Domestic Product
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IMP	Investigational Medical Product
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *(National Authority of Health Medicines and Products)*
OS	Observational Study
PI	Principal Investigator
RNCE	Rede Nacional de Comité de Ética *(National Network of Ethics Committees)*
RNEC	Registo Nacional de Estudos Clínicos *(National Register of Clinical Trials)*
R&D	Research and Development
SAE	Serious Adverse Event
SAM	Sistema de Apoio ao Médico *(Medical Support System)*
SC	Study Coordinator
SOP	Standard Operation Procedure

Chapter 1 – Introduction

This training report represents an overview of a curricular training experience as a study coordinator (SC) at Blueclinical Ltd., which is encompassed in the Master's degree in Pharmaceutical Biomedicine by the University of Aveiro, Portugal.

The internship started on 1st September, 2014 and lasted up to April 2015. During this period I held a SC position in Centro Hospitalar do Baixo Vouga, E.P.E., in Aveiro, Portugal (CHBV), one of the clinical research sites of Blueclinical Ltd.

During my curricular training period, I had the opportunity to follow and to participate in different stages that involve the coordination of clinical trials (CTs) and observational studies (OSs).

Thus, I could participate in the whole process that involves the selection of the site to participate in a specific study, i.e. assignment of the confidential disclosure agreement, presentation of the synopsis or final protocol to the Principal Investigator (PI), as well as site's feasibility evaluation. Furthermore, it was also possible to follow the whole process that is behind the site initiation and approval process and observe how studies are submitted to the administration board of the site and which documents are needed to the submission. After the study site initiation visits, I could participate in all the important procedures relating to the management and coordination of the studies, such as: screening of potential subjects and their randomization, completion of the different procedures of study visits, process, store and send biological samples, report adverse events (AEs) and serious adverse events (SAEs), notify all protocol deviations and so on.

This document is organized in five chapters. This chapter includes an overview of Blueclinical's structure, and the curricular training outcomes. State of the art of clinical trials, description of national and international laws and regulations, and a description of the current state of CTs in Portugal corresponds to the chapter 2. Following this, I describe in detail the activities developed during the training period (chapter 3).

The fourth chapter includes the discussion of the curricular training, where the main difficulties that I felt and the learning outcomes achieved are analyzed. The last chapter corresponds to the conclusion.

1.1. Host Company Overview

Blueclinical – Investigação e Desenvolvimento em Saúde, Ltd. is a partner company of Bluepharma established in May 8th 2012.

Three business units form this company, which are: Phase I, Research and Development (R&D) and Clinical Research Partnership (CRP).

A Phase I clinical trial unit located in Hospital da Prelada, in Oporto, conducts phase I studies in healthy volunteers and early proof-of-concept studies in selected patient populations. This unit has 29 hospital beds to receive volunteers who are accompanied by a wide variety of clinical staff which includes physicians, nurses, clinical coordinators and technicians [1].

The R&D unit was established in order to support companies and institutions on the development of their R&D projects [2].

Finally, CRP unit aims to promote growth of clinical research partners and support them in their activities. For this purpose, clinical study coordinators (CSCs) are integrated in different national clinical research sites [3].

Clinical research sites that are part of CRP are spread across the country, from north to south, and according to data relating to June 2015, CRP partners with Northern Regional Health Administration, which comprehends the primary care units, and 10 hospitals, namely: *Centro Hospitalar do Alto Ave, Centro Hospitalar do Baixo Vouga, Centro Hospitalar de Trás-os-Montes e Alto Douro, Centro Hospitalar da Cova da Beira, Centro Hospitalar de Leiria, Centro Hospitalar de Vila Nova de Gaia, Hospital Distrital da Figueira da Foz,Hospital Garcia da Orta, Unidade Local de Saúde do Alto Minho,* e *Unidade Local de Saúde de Matosinhos*.

During this curricular internship, I had the opportunity to develop activities related to CSC functions at the center CHBV.

CHBV is a district hospital that serves the population of Aveiro, Águeda, Oliveira do Bairro, Albergaria-a-Velha, Ílhavo, Vagos, Sever do Vouga, Murtosa and Estarreja. The mission of CHBV is to provide healthcare to its patients, with efficiency and quality, within a framework of sustainable economic and financial development.

In CHBV, training and research service has already been implemented in the Hospital since 2009, to provide support for the coordination and conduction of CTs and OSs. However, the protocol signed between CHBV and Blueclinical in 2014 was designed to attract more CTs and research funds and provide logistical support to carrying out the studies.

The main departments of CHBV that collaborated with Blueclinical most were: cardiology, endocrinology, pneumology, rheumatology, oncology, surgery and infectious diseases.

This partnership between the Hospital and the Company originated the CTs Support Office (*Gabinete de Apoio aos Ensaios Clínicos* - GAEC), clinical research office responsible for clinical research and OSs in CHBV.

1.2. Curricular Training Outcomes

At the beginning of my internship, I defined a set of outcomes for this curricular training, which were:

- To acquire skills and qualifications in coordination of clinical research;
- To apply and complement the previously acquired academic knowledge in a clinical research context;
- To obtain better understanding of the pharmaceutical research reality;
- To develop and improve personal and soft skills, i.e. written and oral communication, critical thinking, autonomy, self-confidence, sense of responsibility, organization and problem solving;

Furthermore, I also established the following objectives:

- To establish a working contact network;
- To identify potential areas of interest within the pharmaceutical industry.

At the end of training, I verified if my professional and personal goals were achieved.

Chapter 2 – State of the Art of Clinical Research

Significant improvements in health indicators, medical advances and increased longevity in the last decades is a direct result of improvement of supportive care but also of access to innovative health technologies, due to complex and rigorous R&D processes [4].

In countries where clinical research has already reached high levels of maturity, the development of new therapies has a direct influence on the quality of life of the population and continuing improvement of health care. On the other hand, has also contributed to the creation of wealth through the creation of direct and indirect jobs, the increase in Gross Domestic Product (GDP) and improving the trade balance [4].

The first section of this chapter includes a brief description of the drug discovery and development process, including the different phases of CTs. The second section is an overview of the national framework of CTs in Portugal, focusing on national legislation goals and the main barriers that causes the loss of competitiveness of Portugal in the clinical research sector.

2.1. Drug Discovery and Development Process

The development of a new therapy follows a time-consuming and a quite strict investigation process structured into two major steps: discovery and development [4]. This process can last between 10 and 15 years and involve an investment of 1,000 million euros [4].

The discovery stage is characterized by identification of therapeutic targets, validation of the role of the new molecules and extensive study of disease [4]. By following a set of procedures and tests that allow the researchers to ensure proper safety assessment and optimization of molecule or compound properties, they seek to discover a molecule capable of acting upon the therapeutic target and change the course of disease [4]. Later, the new drug is tested in cells and animals through preclinical tests in order to collect data that allow extrapolating of safety information for the transition to clinical phase [4]. This phase may last from three to six years. A

total of five thousand to ten thousand molecules or compounds only 250 will reach the preclinical stage and five on the development stage [4].

The development stage corresponds to the activities developed during the clinical research [4]. Clinical research is research that directly involves human beings, or uses materials from humans and helps translate basic research (done in labs) into new treatments and information to patients benefit [5, 6].

There are two main types of clinical research: OSs and CTs, also called interventional studies [7].

In an OS, participants may receive interventions or procedures as part of their routine medical care, but they are not assigned to specific interventions [7]. According to a research plan or protocol, investigators assess health outcomes in volunteers [7].

A CT follows a pre-defined plan or protocol, according to which participants receive specific interventions [5, 7]. CTs may compare a new investigational product to no intervention, to a placebo, or to a standard treatment that is already available in the market [7]. Through the CTs, investigators try to determine the safety, tolerability, and efficacy of the new intervention by measuring certain outcomes in the volunteers [7]. Subjects participating in CTs are volunteers and cannot play a more active role in their own health care by taking part in CTs [5]. However, they can have access to new treatments and help others by contributing to medical research [5].

CTs are often described by temporal four phases (I-IV), according to traditional division. However, this classification is not adequate since one type of CT may occur in several phases, which the conduction of adaptive CTs [8]. Thus, a classification system based in study objectives is preferable [8].

Figure 1 represents the CTs in the development stage of new drugs.

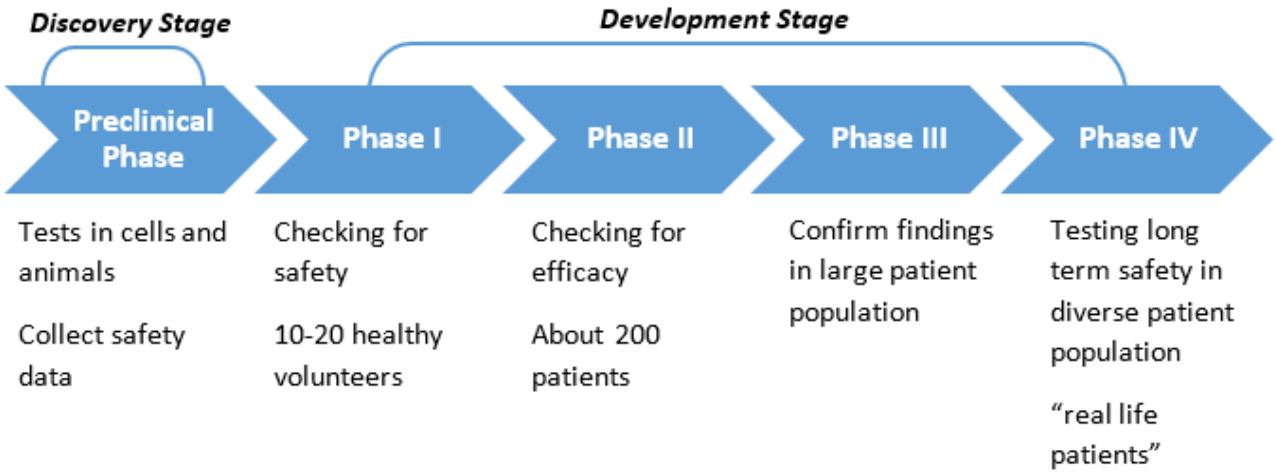

Figure 1. Drug discovery and development (adapted from [4])

In turn, the Table 1 presents the classification of CTs according to objective, study population and phases.

Table 1. Description of CT phases (adapted from [8, 9])

Type of study	Description
Human Pharmacology Phase I	Clinical pharmacology in small numbers of healthy non-patient volunteers in order to assess tolerability, pharmacokinetics and pharmacodynamics, drug interactions, drug metabolism and estimate drug activity [9]. Drugs with significant potential toxicity are usually studied in patients [8].
Therapeutic Exploratory Phase II	Phase II can be divided in two phases: -Phase IIa: clinical pharmacology in small number of patients (10-200) with the target disease (homogeneous and closely monitored population), in order to assess pharmacodynamics, pharmacokinetics and dose-response relationships [9]. The focus is to prove the hypothesized mechanism of action and demonstrate early signals of product's efficacy – also called proof-of-concept or proof-of-mechanism studies [10]. -Phase IIb: larger trials are performed in several hundred of patients to formally assess the dose-response relationship and increase understanding of tolerability, safety and efficacy [9].
Therapeutic Confirmatory Phase III	Randomized controlled therapeutic trials in hundreds or thousands of patients in different stages of disease are performed to test efficacy and safety of two or more dose levels, to compare new drug with existing ones, and to establish dose-response relationship [8, 9]. It usually consists in an international programme (multicenter trials) and adequate basis for assessing the benefit/risk relationship to support licensing are provided in this phase [8, 9].
Therapeutic Use Phase IV	Post-marketing studies are performed in the target population, with wide entry criteria, to broaden experience in clinical practice and enhance understanding of benefit/risk relationship in general or special populations and/or environments objectives [9].

Nowadays, a phase 0 can be also considered. This phase consists of an exploratory study with no therapeutic or diagnostic goals, such as screening studies or microdose studies [11]. Phase 0 involves a very limited human exposure to the

drug where sub-therapeutic doses are used [11]. Phase 0 is intended to speed drug development by quickly excluding ineffective drugs early in the development process [12].

Before starting any procedure of the trial, an informed consent form (ICF) of each subject or the subject's legally authorized representative must be obtained by the investigator.

Through this process, after having been informed of all relevant parts of the trial, subject voluntarily approves his/her willingness to contribute to the clinical research [13]. This decision is documented by means of a written, signed and dated informed consent form [13].

2.2. National and International Laws and Regulations

Activities related with my training are highly regulated in order to protect all parties involved in the clinical trials. For this reason, it is important to have a thorough knowledge of the surrounding regulation and know how to apply it.

During the Master's Degree I received some training regarding on such laws, and when I arrived at Blueclinical Ltd., these issues were also addressed.

The Table 2 is a representation of the main international and national applicable laws and regulations in clinical research by which all members of the research team must be followed.

Table 2. Main international and national regulatory framework for clinical research [13-23]

Regulatory framework	Description
European laws and regulations	
Declaration of Helsinki [14]	Ethical principles for medical research involving human subjects [14].
ICH Topic E6 [13]	Guideline for GCP that provides an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of CT, and is applicable to all protocols involving participation of human beings.[13].
Directive 2001/20/CE of 4th March 2001 [15]	Related to the approximation of the laws, regulations and administrative provisions of the Member States and to the implementation of GCP in the conduction of CTs on medicines for human use [15].
Regulation (EU) No. 536/2014 [16]	Entered into force on 16 June 2014 but will apply no earlier than 28 May 2016. This regulation repealing Directive 2001/20/EC and ensures that transparent information of each CT carried out in the European Union (EU) is made publicly available and that the rules for conducting CTs are consistent throughout the EU [17].
National laws and regulations	
Law No. 46/2004 of 19th August 2004 [18]	Approves the conduction of CTs of medicinal products for human use.
Decree-law No. 102/2007 of 2nd April 2007 [19]	Lays down the principles and guidelines of GCP as regards Investigational Medical Products (IMPs) for human use, as well as special requirements for authorization of the manufacture or import of such products [19].
Law No. 21/2014 of 16th April 2014 [20]	Covers all clinical research with humans including not only CTs with medicinal products for human use but also studies with cosmetics, food supplements, medical devices and all kind of OSs and creates a portal (RNEC) for the submission of all the requests for clinical studies. [21].

Apart from that, the law No. 67/98 of 26th October 1998 and the deliberation No. 333/2007 are related to protection of personal data [22] [23].

Through initiatives of the Member States of EU system, important leads has been provided with the implementation of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 1990 [9].

ICH's mission is to achieve harmonization in order to ensure safety, efficacy and quality of medicines that are developed and registered through the development of ICH Tripartite Guidelines [24, 25].

In order to achieve marketing authorization for a particular human medicine, pharmaceutical companies must submit a dossier via European Medicines Agency (EMA) with clinical study reports included to Committee for Medicinal Products for Human Use (CHMP), which is responsible for the assessment of that medicine [26].

The Agency (EMA) is responsible for ensure the application of GCP with GCP inspectors from national competent authorities [26].

The national regulatory framework and the sector policy is defined by the State of the country that includes que entities responsible for the regulation of the sector, which are INFARMED, Ethics Committee for Clinical Research (CEIC) and CNPD:

- INFARMED is a national competent authority, responsible for CTs applications approval in the Portugal [4].
- CEIC is an independent body that provide a favorable opinion about protocol, investigator(s), facilities, and the methods and material to be used during the trial [13].
- CNPD is an independent committee that supervise and monitor the CTs data regarding the protection of personal data with strict respect for human rights and freedoms.

2.3. Current State of Clinical Trials in Portugal

The new law of clinical research (Law No. 21/2014), which transposes into national law the European directives on the matter, was approved in April 2014 [27].

The goal of this new legislation is to promote clinical research in Portugal and increase competitiveness and transparency in this sector. Through this legislative change, the Government puts forward a new framework for research, creating a National Network of Ethics Committees (RNCE) and a National Register of CTs (RNEC). At the same time, intends to contribute to decrease evaluation and decision deadlines, streamlining the entire process of approval of CTs. Thus, the period for assessment by National Authority of Health Medicines and Products (INFARMED) was reduced to 30 days, while National Committee for Data Protection (CNPD) now has 15 days to make a decision [27].

However, the regulation does not solve all the problems of competitiveness in the field of clinical research: it is important to motivate even more the health professionals, and it is necessary to be aware that in some institutions the approval of CTs is a very time consuming process due to internal management bodies.

According to the data of 23 March 2015, have already been submitted to the INFARMED 18 applications for authorization of CTs and 27 applications were allowed [28].

Available data show that 2006 was the year with more trials submitted and validated (147 trials authorized). Since 2008, the number of clinical trial applications (CTAs) has decreased and only last year (2014) the number of submitted trials was increased slightly (127 CTAs submitted) [28].

In Table 3 are displayed data relating to CTs applications submitted to INFARMED in the last eight years [29].

Table 3. Annual statistics of CTAs submitted to INFARMED (data representation from [29]**)**

CTA	2006	2007	2008	2009	2010	2011	2012	2013	2014
Submitted	160	136	146	116	107	88	118	114	127
Authorized	147	131	138	116	105	87	99	116	119
Not authorized	1	0	0	0	2	0	0	0	3
Average time for authorization (days)	-	45	43	42	42	41	40	38	33

The explanation for this CTs decrease is that the large pharmaceutical companies are phasing out Portugal from the list of countries where they want to conduct CTs [30].

A number of barriers has caused Portugal's loss of competitiveness in this sector:

- Policy and industry strategy - The central problem is the lack of vision for clinical research and the creation of implementation mechanisms [4].
- Regulation and legislation - Portugal lost competitiveness compared to other European countries because the average time for approval of CTs exceeds 70 days (according to the previous legislation) and this time does not include the approval by the administration board of the trial site, which is essential to start the trial [4]. In many European countries, the responsibility for data protection is the sponsor's responsibility and does not require CNPD authorization as happens in Portugal [4].
- Organization and infrastructures - Hospital administrations don't include conducting of clinical research activities in the strategic objectives adopted in

the organizations and CTs are often regarded as an activity that generate costs [4]. The absence of CTs support structures leads to a lack of center efficiency and is responsible for poorly distributed tasks and a large overhead of the investigators [4].

- Incentives, training and career - Lack of training and awareness of hospital administrators, doctors, nurses, pharmacists, technicians [31].

The promotion of clinical research in Portugal will generate quality data for healthcare decision support; adoption of best practices in monitoring of patients; job creation and funding for the country and institutions [4].

Chapter 3 – On-the-job training

This chapter describes the different training sessions attended during my training period, as well as the theoretical knowledge acquired during the same.

When I arrived at Blueclinical Ltd., I was introduced to organization and infrastructure of the host institution. During the first weeks, I was given an overview of the hierarchical structure of Blueclinical Ltd. and I was introduced to the CTs that were part of the CHBV set of active studies.

The main activities developed during my internship happened in the context of Blueclinical CRP business unit, and correspond to coordination of CTs.

In this chapter, I will provide a detailed description of the procedures followed during the internship to perform the requested tasks and activities.

As a SC trainee, I had the opportunity to follow the whole cycle of activities involved when performing a clinical trial.

This way, the current chapter is divided in three sections, each related to the main activities developed during the internship and the theoretical knowledge acquired. First section focuses on the main functions of each member of clinical research team.

The activities that I developed as SC related with site selection, submission of documents to regulatory authorities and site initiation are described in detail in the second section.

Other continuous activities that I performed as SC such as adjustment of internal documents, Good Clinical Practice (GCP) trainings, control of CTs stocks and direct communication with the monitors is the last section of this chapter.

3.1. Clinical Research Team

During the first weeks, I was reminded of the many intervenients in a research team and their roles. The complexity of research and development of new drugs in CTs phase requires the involvement of a diverse set of stakeholders as demonstrated in Figure 2 [4].

Figure 2. The main stakeholders in clinical research (adapted from [4])

Sponsor is responsible for the initiation, management or financing of a CT [13].

A trial site or clinical trial center can be a public or private health organization, a laboratory or other entity with appropriate human and technical resources to conduct

CTs [4]. The administration board of the center is responsible for CTs approval in the trial site.

The conduction of CTs at a trial site is the responsibility of the PI who also leads the investigational team [13].

The investigational team can include medical doctors, which are PIs, and sub-investigators, pharmacists, nurses, study coordinators, diagnosis, laboratory and therapeutic technicians.

Another important stakeholder is the patient who could benefit from the investigational drug [4].

During the conduction of clinical trial, monitors or Clinical Research Associates (CRAs) are responsible for supervising the progress of a CT and ensuring that it is conducted, recorded, and reported properly, according to the existing regulations, standards, guidelines and protocol [13].

The investigational team works closely with CRAs that integrate Contract Research Organizations (CROs) and the purpose of each qualified professional who is part of the trial is to ensure that “rights, integrity and confidentiality of trial subjects are protected, and data and reported results are credible and accurate” [4, 13]. All elements of the research team must receive qualified training in ICH-GCP principles.

The interactions between various stakeholders that contribute for the conduction of CTs are represented in Figure 3:

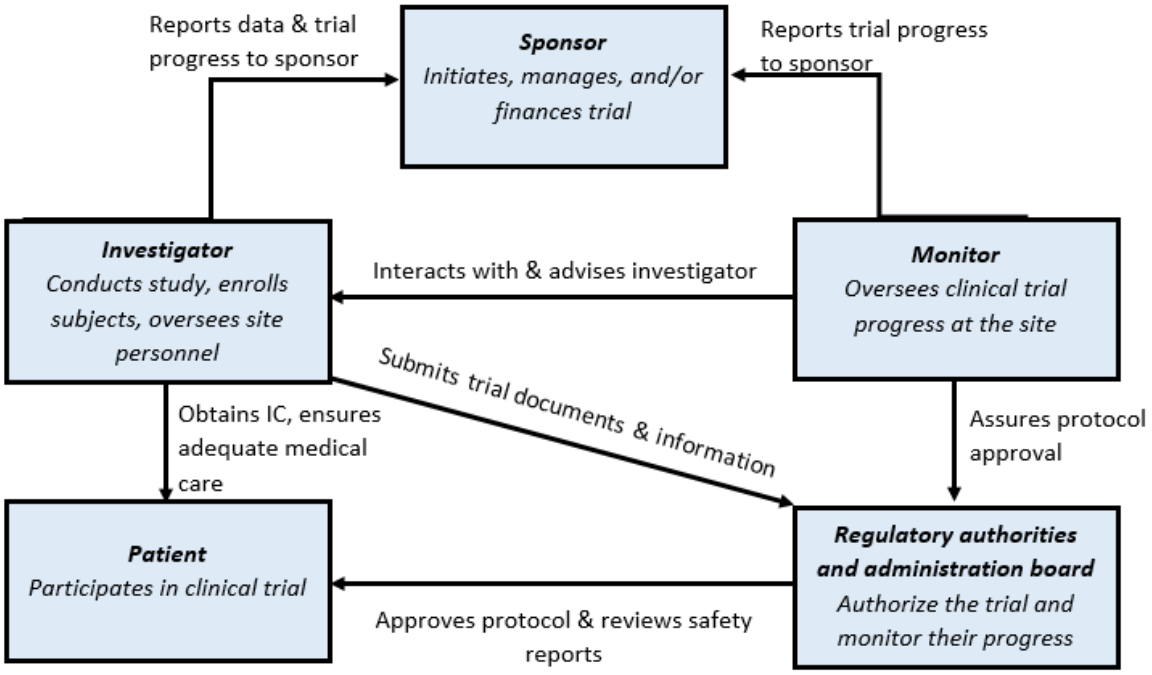

Figure 3. Interactions between stakeholders of the CT [4].

3.2. Activities Developed as a Study Coordinator

As a study coordinator, my role was to support the three key phases of clinical trials: site selection, regulatory authorities' submission, and site initiation.

Firstly, for a better understanding of the steps of the whole process, a flowchart of clinical trial steps in which a SC is involved is presented in Figure 4.

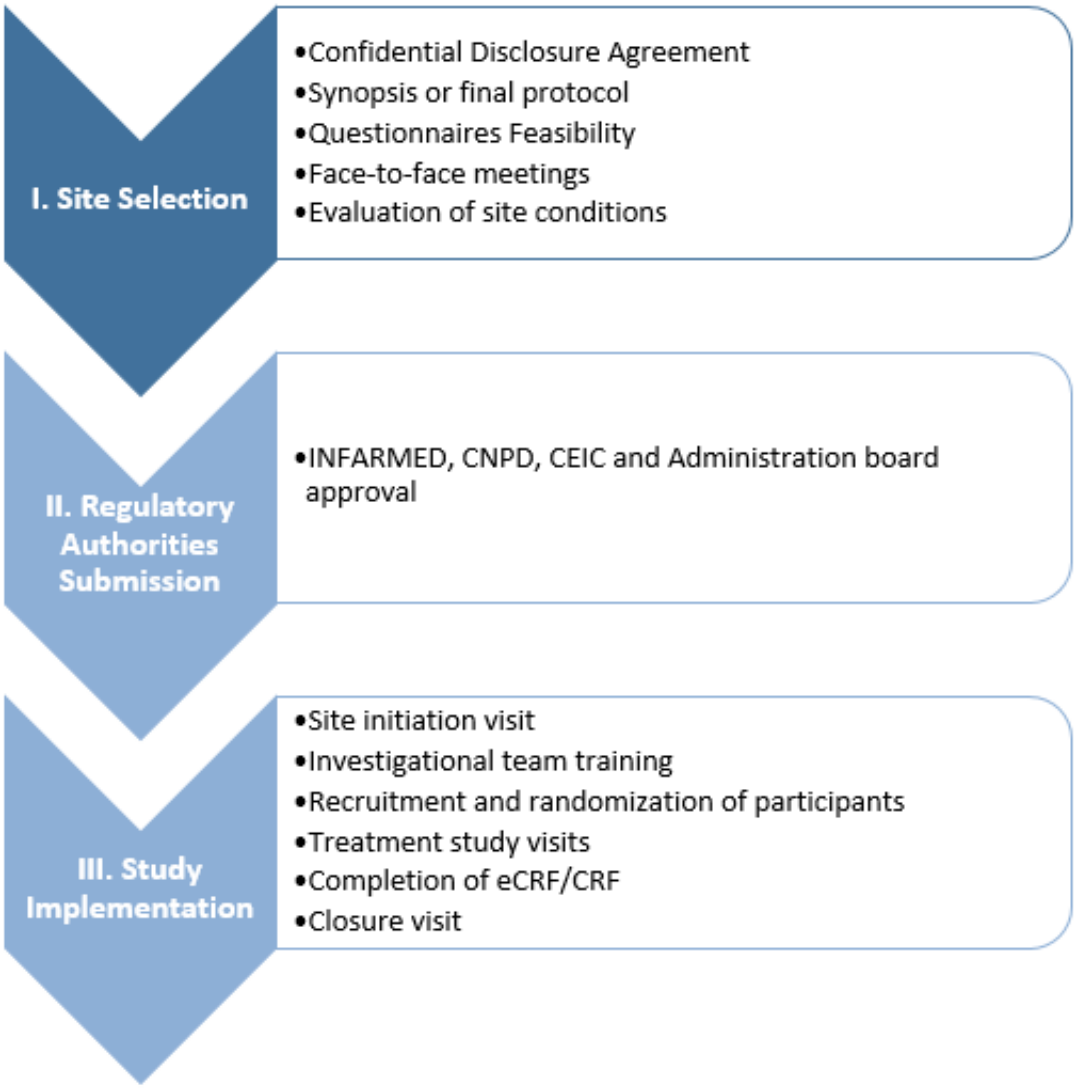

Figure 4. Representation of the main clinical trial steps in which a SC is involved.

I. Site Selection

The first contact with SC about the possibility of the site selection for a particular CT occurs through Blueclinical network, or directly from the sponsor through the monitors involved in the trial.

Firstly, the PI signs the Confidential Disclosure Agreement in order to be able to have access to synopsis or final protocol of the study. Then, it is up to the SC to present the feasibility of the trial to PI in order to evaluate if the site has all the conditions to conduct the trial.

The next step is the face-to-face meeting with the monitor or person designated by sponsor, the PI and SC. In these visits, the PI gives his opinion regarding the protocol and raises issues that may have emerged in the meantime.

In order to confirm that resources and facilities are in compliance with GCP, a tour around center facilities can be made.

During my internship, I had the opportunity to participate in this process and I realized that an effective response is a remarkable fact for the site selection and that it is always very important to provide reliable estimates.

II. Regulatory Authorities Submission

The regulatory authorities must approve a clinical trial before it initiation. Thus, the information about a CT must be sent to the INFARMED, CNPD, CEIC and to the administration board of the trial center. During my internship, I could perform different duties related to the CTs submission, such as:

- Review the financial contracts.
- Collect all site-related documentation required for CT application to regulatory authorities.
- Submit the CT dossier to the site administration board.
- Collaborate with investigational team in prescreening activities, if applicable.

III. Study Implementation

Officially, the initiation of CT begins with the site initiation visit. The role of this visit is to discuss with the entire investigational team the protocol, the inclusion/exclusion criteria, study procedures and strategies of subjects' recruitment [32].

Important documents like the *Curriculum Vitae* of the different members of investigational team should also be obtained in this visit.

During this stage, the SC should support all the monitor activities in order to make this visit more productive.

After this meeting, the investigators can start with the recruitment process of participants.

The sponsor provides specific online training at the beginning of CT so that each element be familiar with the procedures. These online trainings are mandatory for every element of investigational team.

After receiving training in the clinical trial protocol in this visit and before the recruitment of the subjects, was reinforced to me the importance of study intensively the protocol of specific CT.

Thus, in detail, each protocol was analyzed, and one of my functions was to create and display worksheets for each member of the investigational team. During the course of clinical trials, the existence of worksheets of each trial is very important. Since not all companies have a habit to provide worksheets to the research team, I have made many of them.

CT worksheets are specific documents that summarized relevant information for each investigational element (general information of the trial, visit procedures, what to do in case of AEs or SAEs, specific procedures related to withdrawal of consent to participate in the CT or specific procedures in case of pregnancy, concomitant medications, preparation of the medication if necessary…).

To create worksheets a very complete and critical analysis of the protocol is necessary.

A careful translation from English into Portuguese, because not all of professionals involved in the trial are comfortable with English, must also be taken into account in order not to change the meaning of the protocol.

Commonly are created worksheets for each visit of the trial, for concomitant medication, prohibited medication, inclusion and exclusion criteria, worksheets that explain what to do in case of subject withdrawal or exclusion of the trial, and worksheets that describe specific procedures of the trial to nurses, technicians and researchers.

The functioning of each CT depends on the research team involved. However, in most CTs, pre-screening of possible participants is also SC’s responsibility. Thus,

through the internal Medical Support System (SAM) of CHBV, I had the opportunity to perform pre-screening of potential candidates for a specific clinical trial.

The subjects only can be randomized to the trial if they meet all the eligibility criteria after the screening period. This means that participants must meet all the inclusion and none of exclusion criteria of a specific study protocol to which they volunteer.

After the subject randomization, the treatment study visits begin, according to the protocol.

During each clinical trial visit, it is essential that the investigational team feel that they have the support of the study coordinators in case of any doubt. Thus, it is SC responsibility to be alert to all procedures performed during the visit if the investigational team deems necessary.

Specific procedures must be strictly performed for each visit according to the protocol of the CT. A few examples of CT procedures are:

- Obtain the ICF, demographics and medical history (e.g. gender, age, birth date, race, any clinically significant condition, alcohol and drugs use),
- Physical examination (e.g. height, weight),
- Vital signs (e.g. blood pressure, heart rate, body temperature),
- Exams (e.g. electrocardiogram, X-ray, echocardiogram),
- Clinical laboratory tests (e.g. urinalysis, coagulation, chemistry, haematology),
- Concomitant medication, AEs and/or SAEs,
- Questionnaires of quality of life assessment,
- Dispense the study medication,
- Process laboratory samples and prepare the shipment to be send to the central laboratory.

My major role was to support CT visits, guiding the investigational team so that the process of the visits be undertaken efficiently and quickly, in order not to take too much time to patients or to professionals involved in the research team.

It is a very rewarding work but also very demanding, since any failure on the part of SC could compromise the work of the whole team. It is therefore very important to study the protocol in detail and clarify any questions that may exist.

Another important function of the SC that I had opportunity to perform is the completion of Case Report Form (CRF) or electronic Case Report Form (eCRF) of each clinical trial visit.

All visits must be introduced in the CRF and must be derived from source documents. Source documents are the original documents, data and records (e.g. hospital and clinical records, laboratory notes, x-rays…) and the CRF information must be consistent with these records [13].

Therefore, I was trained in the data entry and resolution of queries in order to learn how to handle different types of eCRFs and CRFs.

The end of this stage is characterized by closure visit that can be performed when:

a) Subjects are no longer being dosed
b) All data have been collected
c) The database is locked and ready for statistical analysis
d) Study conduct has ended
e) Sponsor decides to finish the trial [33].

In this visit, the monitor should ensure that the CT documentation is well organized and will remain intact and be accessible in the future as needed for regulatory reasons [33]. If thorough and accurate records are not maintained, the PI cannot prove that the study was conducted in accordance with the protocol and applicable regulations and that subject safety was adequately monitored throughout the conduct of the trial [33]. It is SC function to assist the monitor in this role.

3.3 Continuous SC's Activities

Good Clinical Practice

Being complaint with ICH-GCP's is the principal requirement for people who work in clinical research.

During this experience, I had a chance to take an online course "Essential Good Clinical Practice", by Brookwood International Academy, which is a GCP training programme with examination for the Certificate in Essential GCP. The modules of the GCP training covered the principles of GCP and the fundamental requirements relating to subject protection (ethics/consent), safety reporting, study protocol, data recording, investigational product, trial documentation, retention and archiving. These online trainings are extremely important for the whole research team because it is mandatory to comply with GCP standards in the daily practice of CTs.

At the beginning of each CT, new GCP online trainings were held in order to always keep in mind recurrent procedures.

Adjustment of Standard Operation Procedures (SOPs)

I also could adapt internal documents (SOPs) to que center in which I was allocated (CHBV).

One of the Blueclinical goals is the harmonization of documents by Blueclinical network, so that each center and back-office always has the necessary standard documents available, which will only need to be adapted to different studies and clinical trials.

Thus, the adaptation of such documents included the placement of logo, updating the information relating to financial contracts plots, names of the parties responsible to the administration board and dates of when the SOPs are effective.

This experience allowed me to study each document in detail.

Control of study and lab materials stocks

Furthermore, in order to avoid missing of study material, accumulation of kits or study medication outdated, I could manage the stocks periodically to ensure that all necessary study and laboratory materials are available during the different procedures of the trial.

Communication with the sponsor, monitor and, when applicable, with the regulatory authorities

Throughout the course of the clinical trial, it is important to maintain continuous contact between all the entities involved.

Since the monitors are responsible for establishing the communication between sponsor and investigational team, the communication with them was performed numerous times during the trial by telephone, e-mail or face-to-face.

The contact between investigational team and monitor can be established through the study coordinator, and my internship experience shows that it may be necessary to contact the monitor for:

- Clarify doubts of the protocol,
- Request dry ice, study and laboratory material,
- Report SAE,
- Receive and send clinical trial documents,
- Prepare monitoring visits,
- Ask for opinion in the situations of the trial that the protocol does not contemplate,
- Inform monitor of the study status.

Chapter 4 – Discussion

The CTs are the current gold standard for obtaining the required data to ensure the well-being, safety and quality of patient's life [9]. The performance, efficacy and safety of new drugs in human body can be tested through clinical trials.

During my internship, I had the opportunity to develop my knowledge in the field of clinical research through the conduction of CTs as described in the previous chapter.

Thus, I experienced activities that allowed me to grow professionally in clinical research area as a SC. Developing this set of tasks provided me a complete training experience in the context of CTs coordination.

From the beginning of my internship, I had the opportunity to work in different departments dedicated to research, perform several activities, learn with senior professionals and be in touch with the patients.

When my training begins, I did not realized that I was going to interact directly with patients. At the beginning, it was a little bit difficult to relate myself with patients, but I could overcome quickly this difficulty and stablish a very good relationship with the most of the patients. I realized that all the volunteers that participate in CTs expect to feel confidence by the research team, so it is very important to perform continuous monitoring of the participants and show them that we are entirely available for any questions or issues that may arise.

Furthermore, I could improve my oral communication ability due to the daily contact with stakeholders and members of clinical research team. Adjustment of SOPs and daily contact essentially via e-mail with monitors allowed me to develop my writing skills.

One of the main difficulties was without doubt the lack of knowledge regarding to the more specific medical terms in each area.

I felt the need to do harder work at home in order to be able to understand the meaning of each sentence of the protocol.

As each protocol is specific to a certain pathology, and although my degree allowing me to have a general background of medical terms and their meaning, not everything was approached during my academic journey.

Thus, homework was done and I quickly realized that this difficulty can be easily overcome after a very detailed study of each protocol and research of each term that is not of my knowledge.

Because every day of the training was a challenge, it was possible to apply and complement concepts that was previously acquired during my academic journey in a clinical research context and get prepared for the real world of clinical trials.

I could deal directly with the laws and regulations of pharmaceutical research, guidelines and GCP, which is part of the day of any SC. I consider that my master was crucial to understand quickly and effectively the functions that were imposed to me, since all concepts covered during the internship with regard to clinical research, had already been discussed during my Master.

As a SC trainee, I had to work with a large number of professionals and manage several activities that were my responsibility. In order to ensure that nothing would be forgotten, I had to improve my organizational skills. Thus, I get an agenda for this purpose in order to record all the activities for which I was responsible. Furthermore, on the eve of patients' visits of the trial or other important meetings and activities, I made sure that all that I needed was available, prepared, well-organized, dated and signed correctly. Safety and well-being of patients are the central role of clinical research, such as the quality of clinical data obtained. Therefore, I become more exigent with my work and developed a high sense of responsibility.

There are several tasks involved in coordination of clinical trials. However, there may occur mishaps and new developments that require new decisions and set priorities, such as:

- It is usual that during a certain task, the SC receives a phone call from the investigator asking for support for the recruitment of volunteers who may be eligible for the trial;
- Monitors can send information of a new trial or study and the SC have to present that information to a potential investigator;

- AEs or SAEs may occur and the investigational team should report as soon as possible.

Therefore, one of the most important things of the SC's work is to establish priorities and deadlines, as all the tasks have to be done with highest quality. In order to overcome some unpredictable situations, a problem solving was another skill that I needed to improve, such as critical thinking.

Because of daily contact with a large number of professionals, I had the opportunity to improve my knowledge in several areas and discover other important areas of interest. However, during this internship I wished I had established a bigger contact network in clinical research area.

This training showed me the importance of SCs in research team. They are responsible for assisting the monitors; submitting studies, ensuring that the protocol details, laws and regulations are followed; entering data in the platform; managing patients' anxieties and contact with all members of investigational research team, patients and monitors.

In the CHBV, I felt that nearly all the investigational teams were 100% depended on the SC in case of any doubt that might arise. This requires that the SC be prepared to clarify and solve all the issues related to the investigation.

Over time, I understood that each investigational element is gaining autonomy and becomes less dependent on the SC support.

In order to accomplish this task without big difficulties, the intensive study of protocols and clarification of all doubts with healthcare professionals and monitors are essential.

Despite all the difficulties enumerated so far, I believe that the main difficulty was the lack of confidence felt throughout this internship.

I know that this difficulty was responsible for lack of proactivity and initiative on my part.

All the work was done in partnership with SC Diana Soares, so I cannot say that I was responsible for a particular study or trial.

I think this made difficult to develop my personal skills such as self-confidence and autonomy since most of the time I felt that my coordinating role was not as prominent as I wished.

It also can be justified in part by the fact that health professionals are quite resistant to change and not all were available to deal with a new SC because they were already accustomed to a particular type of work, and that is understandable.

I know that the lack of confidence in my work was something harmful to me during the internship and I cannot say that I was able to overcome it.

Next time, however, I know that the best strategy to overcome it will be by assuming the responsibility entirely for a certain project and feel that I have full control of the situation.

According to this experience, I can conclude that the SCs play a very useful role in the research unit and one of the things I have learned was that each investigational team is unique as well as each trial or study. It is impossible to draw a set of general coordination methods that will apply to any reality. So what I take with me the most valuable of this internship is a set of techniques used in accordance with the teams I worked with, which have to be further adapted to each situation. However, the most important thing that is necessary to remember is that the accuracy and quality of data must appear in every situation, in order to avoid future problems.

Chapter 5 – Conclusion

This report presented the activities developed during my training period at Blueclinical Ltd., as well as the skills and learning outcomes achieved.

During this 7-month period, I had the opportunity to experience the real work environment, as well as to complementing my previous knowledge that I developed during my academic journey, and improve it. Being a SC allowed me to apply all knowledge and tools acquired during the Bachelor's in Biomedical Sciences and Master's in Pharmaceutical Medicine degrees.

This experience has shown me how essential clinical research is to enhance progress in the health area and the importance of the role of SC in CTs conduction.

I believe that my academic background provided me with a range of soft and hard skills that were essential for an easier adaption to the work environment and integration into the working teams.

I consider that this training was a very rich experience for several reasons: interaction with different health professionals with different experiences in the field of CTs; possibility to work with different interventional CTs phases and with various therapeutic indications; possibility to interact with distinct monitors and sponsors; improvement of time management and problems resolution skills, improvement of communication skills.

In addition, the close contact with the patients allowed me to understand their needs during the participation in clinical trials, in terms of information and the level of detail and literacy that should be used during the communication with each patient.

It is very important to transmit confidence to the patient, in order to ensure greater compliance with the protocol.

All members of the investigational team resort to SC in case of doubt, so it is essential to know all the details of the protocol and predict any obstacle that may arise during the trial.

I understood with this experience that the SC’s day is never a routine: new issues and unexpected interruptions are part of the SC daily work. Thus, completing all the activities planned for the next day becomes a challenge, as unexpected tasks arise every time, and priorities for the day may change. In consequence, a SC must have good abilities to work under pressure and must have strong capabilities to resolve problems that may arise quickly, as well as strong communication skills.

I really appreciated my journey in Blueclinical Ltd., and I am very thankful for this opportunity.

Through this experience, I could see how challenging the study coordinator's work is.

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